REMARKS

I. Status of the Claims. No amendments are made to the claims. Claims 36-96 are pending. Of these, claims 44-65 and 74-96 have been withdrawn from consideration by the Examiner as being directed to non-elected subject matter. Accordingly, claims 36-43 and 66-73 are under examination.

It is noted that all prior rejections of the claims under 35 U.S.C. §112, first paragraph for lack of enablement have been withdrawn.

By this Amendment, no new matter has been added to the application.

II. Claim rejections. The claim rejections set out in the Final Office Action are summarized and addressed as follows.

(i) Double Patenting Rejection. Claims 36-43 and 66-73 are provisionally rejected under the judicially created doctrine of obviousness double patenting, as obvious over certain claims of co-pending application no. 10/001,245. Applicants confirm that the aforementioned co-pending application has not issued as a patent. Accordingly, Applicants are not required to respond to the rejection at this time.

(ii) Rejection Under 35 U.S.C. §112, first paragraph (written description). Claims 36, 38-43 and 66-73 remain rejected for alleged lack of written description. The rejection is traversed. On April 11, 2008, the USPTO issued updated patent examiner training materials on the written description requirement ("the new training materials," available at http://www.uspto.gov/web/menu/written.pdf). The new training materials are incorporated into the Manual for Patent Examining Procedure. *See* USPTO announcement available at http://www.uspto.gov/main/pat_exm_trng.htm. Application of the new training materials demonstrates that the application provided sufficient information to show that Applicants were in possession of the claimed invention when the application was filed.

The new training materials set forth that in determining whether one of ordinary skill in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time the application was filed the Examiner should determine, for each claim:

a. Actual reduction to practice

b. Disclosure of drawings or structural chemical formulas

c. Sufficient relevant identifying characteristics, such as:

i. Complete structure

ii. Partial structure

iii. Physical and/or chemical properties

iv. Functional characteristics when coupled with a known or disclosed correlation between function and structure

d. Method of making the claimed invention

e. Level of skill and knowledge in the art

f. Predictability in the art

Revised training materials at page 1.

Focusing first on claim 36, consideration of these factors establishes that the Applicants were in possession of the claimed invention when the application was filed, as follows.

Claim 36 is directed to a genus of recombinant *Bet v 1* allergens derived from a naturally-occurring *Bet v 1* allergen from the order *Fagales* that have (a) a substitution of a solvent-accessible amino acid residue that is conserved among *Bet v 1* homologous allergens within the order *Fagales*, said substitution occurring in a B-cell epitope of the naturally-occurring *Bet v 1* allergen; (b) reduced specific IgE binding compared to the naturally-occurring *Bet v 1* allergen from which the mutant allergen is derived; and (c) an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of the naturally-occurring *Bet v 1* allergen.

1. Actual reduction to practice. The instant application discloses and characterizes three independent recombinant mutant *Bet v 1*, the single point mutants, Glu45Ser and Pro108Gly, and the double point mutant, Asn28Thr + Lys32Gln, and a fourth recombinant mutant *Bet v 1* bearing the combination of each of the aforementioned four point mutations, the so-called "triple patch mutant," Glu45Ser, Asn28Thr + Lys32Gln, Pro108Gly. Each of the disclosed and characterized recombinant *Bet v 1* allergens had the properties of the claimed allergens, i.e., they reduced IgE binding and retained a preserved α-carbon backbone compared to native allergen. Thus, the application discloses four examples in which the genus of claim 36 was reduced to

practice. In addition, the application discloses that point mutations Thr10Pro, Asp25Gly, Asn47Ser, Lys55Asn and Thr77Ala are incorporated into recombinant mutant *Bet v 1* mutant allergens.

2. Disclosure of drawings or structural chemical formulas. The application sets forth the sequence of *Bet v 1* in Fig. 3, along with the precise position of the aforementioned mutations. Thus, the application discloses the structural formula of the exemplified mutants.

3. Identifying characteristics.

(i) Complete structure. The Application sets forth the complete structure of the exemplified mutants.

(ii) Partial structure. Each of the recombinant mutants of claim 36 is derived from the *Bet v 1* sequence set forth in Fig. 3. Thus, the application includes a partial sequence for each of the recombinant *Bet v 1* allergens of claim 36.

(iii) Physical and/or chemical properties. The genus of allergens encompassed by claim 36 are substitutions of amino acids that are conserved among *Bet v 1* homologous allergens within the order *Fagales*, said substitution occurring in a B-cell epitope of said naturally-occurring *Bet v 1* allergen. Moreover, the pre-existing general knowledge in the art supplements the description: One of ordinary skill in the art the art would thus readily understand that "substitution" refers to the replacement of a *Bet v 1* amino acid with another of the other 19 amino acids. The application further sets out that amino acids to be substitued are located on the surface. Such amino acids have a solvent accessibility (water) of at least 20%, preferably 20-80% and more preferably 30-80%. *See* specification at page 19, lines 30-35. A further preference is the substitution of a polar residue for another polar residue and a non-polar residue for another non-polar residue. The amino acid to be substituted is further identified as a "residue that is conserved among *Bet v 1* homologous allergens within the order *Fagales*." *See* claim 36. The specification sets forth that "major birch pollen allergen *Bet v 1* shows about 90% amino acid sequence identity with major allergens from pollens of taxonomically related trees, i.e., *Fagales*." Specification at page 22, line 36 through page 23, line 2. *Bet v 1* proteins are even more highly identical to each other than allergens from taxonomically related trees, e.g. 95-100% identity. Using standard sequence alignment programs available at the time the application was filed, one of ordinary skill in the art could readily align and identity conserved amino acids among the *Bet v 1* allergens from the order *Fagales*. *See*, e.g., specification at page 24, line 23, et seq., section entitled "Sequence

Alignment." Thus, the specification provides certain chemical and physical properties for the substituted amino acids of claim 36. Moreover, the pre-existing general knowledge in the art supplements the description: by the time the application was filed, the three dimensional structure of *Bet v 1* protein had been determined and published. *See* reference to Ghajhede et al., 1996, *Nature Structural Biol.* 3:1040-1045 at page 23, line 25 of the specification. Knowledge of the three dimensional structure allows identification of solvent accessible amino acids. The high level of identity means that using the knowledge of the three dimensional structure of even one *Bet v 1* protein of to identify solvent accessible amino acids and alignment procedures allows identification of the solvent accessible amino acids of any *Bet v 1* allergen from the order *Fagales*. Lastly, recombinant mutant *Bet v 1* allergen of claim 36 has "an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of said naturally-occurring *Bet v 1* allergen," i.e., the recombinant Bet 1 has a native conformation. At the time the application was filed, it was generally known in the art was that replacement of surface amino acids would have a reduced probability of disrupting three dimensional structure. The specification sets out explicitly that amino acid residues having a solvent exposure of less than 20% were "not regarded as relevant for mutagenesis due to the possible disruption of structure." Specification at page 24, lines 17-19. Thus, the specification and the general knowledge in the art provides guidance on the chemical and physical nature of the substitutions to be made in the recombinant allergens of claim 36.

(iv) Functional characteristics coupled with a known or disclosed correlation between function and structure. The mutant *Bet v 1* allergens of claim 38 have the property of reduced IgE binding compared to the allergen from which they are derived. As set forth in the "Background of the Invention," it was general knowledge in the art at the time the application was filed that allergens with reduced IgE binding could be produced by site-directed mutagenesis. See specification and cited references at page 7, line 15, et seq. The specification further discloses that the amino acids available for antibody binding are located on the surface of allergens (see specification at page 19, lines 30-32) and that dominant IgE epitopes, in particular, are typically contained within conserved patches on the surface of allergens (*see* specification at, e.g., page 20, lines 4-13 and page 23, lines 24-36). Thus, the functional characteristic of reduced IgE binding flows directly from (i.e., is "coupled with") the known property of IgE epitopes to be present on the

surface of allergens, particularly in conserved patches on the allergen surface, and the disclosed and well known correlation that disrupting IgE epitopes will reduce IgE binding.

d. Method of making the invention. As discussed in Applicants' previous response filed on August 8, 2007, the specification discloses methods for making the claimed invention. Thus, the specification gives extensive guidance that allows one of ordinary skill in the art to determine which conserved amino acids of a *Bet v 1* allergen from the taxonomic order *Fagales* should be substituted such that the recombinant mutant allergen would have the claimed properties of retaining native structure and exhibiting reduced IgE binding. It is noted that following Applicants' previous response, the Examiner withdraw a prior rejection of the claims for lack of enablement. It is respectfully submitted that withdrawal of the enablement rejection is an acknowledgment that the specification discloses a method of making the invention. It is noted, moreover, although the enablement and written description requirements of section 112, are independent requirements, the Federal Circuit has stated:

> Those two requirements usually rise and fall together. That is, a recitation of how to make and use the invention across the full breadth of the claim is ordinarily sufficient to demonstrate the inventor possesses the full scope of the invention, and vice versa.

Lizardtech, Inc. v Regents of the University of California, 424 F.3d 1336,1345 (Fed. Cir. 2005). *See also Capon v. Eshhar,* 418 F.3d 1349, 1360 (Fed. Cir. 2005) (Although separate requirements, the "legal criteria of enablement and written description are related and often met by the same disclosure.")

e. Level of skill and knowledge in the art. The consideration of the factors set out above demonstrates that the level of skill and knowledge in the art related to *Bet v 1* allergens from the order *Fagles* and IgE epitopes was high. Thus, the state of the was such that it was known, for example, that *Bet v 1* allergens include dominant IgE epitopes and that they reside in surface patches, that *Bet v 1* proteins from the order *Fagales* share a high level of identity and exhibit cross reactivity, and that substitution of amino acids on the surface of *Bet v 1* allergens could disrupt IgE epitopes and lower IgE binding.

f. Predictability in the art. Each of the working examples set forth in the specification has the properties called for in claim 36. Moreover, the specification includes the

results for all of the mutants that had been made at the time the application was filed. Thus, it is apparent that the claimed mutant allergens may be predictably derived using the methods set forth in the application.

In summary with respect to claim 36, the specification discloses *Bet v 1* mutant allergens with the properties set forth in claim 36, provides a partial sequence for each of the claimed mutant allergens in that they are each derived of *Bet v 1* allergens from the order *Fagales*, and provides detailed guidance on the nature of the substitutions to be made in the claimed allergens and the functional characteristics exhibited by the claimed allergen. Moreover, the skill and knowledge in art is high. For at least these reasons, one of ordinary skill in the art would recognize that the inventors were in possession of the genus of claim 36.

The specification similarly provides written description for the other claims:

Claim 66 differs from claim 36 in that it is directed to a recombinant mutant allergen derived from a naturally-occurring allergen within the order *Fagales* that is homologous to *Bet v 1*. The specification sets forth that:

> The major birch pollen allergen *Bet v 1* shows about 90% amino acid sequence identity with major allergens from pollens of taxonomically related trees, i.e. *Fagales* (or instance hazel and hornbeam) and birch pollen allergic patients often show clinical symptoms of allergic cross-reactivity towards these *Bet v 1* homologous proteins.

Specification at page 22, line 36 through page 23, line 6. Based on the level of skill in the art at the time the application was filed, a worker of ordinary skill in the art would have recognized that the high degree of identity among *Bet v 1* homologous proteins from the order *Fagales* and the finding that birch pollen allergic patients exhibited symptoms of allergic cross-reactivity towards these homologous proteins indicates that *Bet v 1* homologous proteins from the order *Fagales* have highly similar primary sequences and three-dimensional structures[1], indicating that the features that are set forth above and which indicate that the Applicants had possession of the mutant allergens for *Bet v 1* proteins from the order *Fagales* also hold for the broader genus of

[1] It is noted that the new training materials include a "Technical Note" stating that "[g]enerally, tertiary structure conservation would be lost when the amino acid sequence varies b more than 50%," citing Chothia et al., The relation between the divergence of sequence and structure in proteins, EMBO J. 5:823-826 (1986). *See* new training materials at page 38.

recombinant mutant allergens of *Bet v 1* homologous proteins from the order *Fagales*. Thus, the specification provides written description for claim 66 for the same reasons it provides written description for claim 36.

The specification also provides written description for the mutant allergens of claims 38-43 and 67-72, which claims depend from claims 36 and 66, respectively. Thus, the general level of skill and knowledge in the art would readily allow one of ordinary skill in the art to use the known crystal structure of *Bet v 1* and/or sequence alignment of *Bet v 1* sequences to identify amino acids that have a solvent accessibility of 20% (claims 38 and 68), are conserved with 70% identity among *Bet v 1* allergens from the order *Fagales* (claims 39 and 69), wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400Å of the surface of said naturally-occurring *Bet v 1* allergen (claims 42 and 72), wherein the solvent-accessible amino acid residue that is conserved among *Bet v 1* homologous allergens within the taxonomic order from which said naturally-occurring *Bet v 1* allergen is substituted with an amino acid that is not conserved among *Bet v 1* homologous allergens within the taxonomic order from which said naturally-occurring *Bet v 1* allergen occurs (claims 43 and 73) and wherein said allergens homologous to *Bet v 1* have an amino sequence that yields a BLAST probability of less than 0.1 when compared to an amino acid sequence of SEQ ID NO: 37 (claim 67). The specification further provides extensive guidance on tests that can be used to determine with recombinant *Bet v 1* allergens have IgE binding reduced by at least 5%, compared to the naturally-occurring *Bet v 1* allergen from which it is derived (claims 40 and 70) and wherein average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant *Bet v 1* allergen and said naturally-occurring *Bet v 1* allergen is less than 2Å (claims 41 and 71). Thus, the Applicants were also in possession of the subject matter of claims 38-43 and 67-72.

Thus, a consideration of the factors set forth in the new training materials on written description, demonstrates that the Applicants were in possession of the full scope of the subject matter of claims 36, 38-43 and 66-72. Reconsideration of the claims and withdrawal of the rejection thereof under 35 U.S.C. 112, first paragraph for lack of written description is requested.

III. Conclusion. This application is believed to be in condition for allowance, which is earnestly solicited. If the Examiner there are remaining issues that could be resolved by an interview or entry of an Examiner's Amendment, the Examiner is requested to contact the undersigned attorney.

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